REMARKS/ARGUMENTS

Support for Amendments

Applicants amend claims 39, 42, 48-51, 55, 58, 59, 63-65, 67, 69, 70-72, 75, 76, 79; cancel claim 68 and provide new claim 80. Support for the amendments may be found throughout the specification as originally filed. Specific support is provided for each claim amendment.

Claims 39 and 42 are amended from "the said cell" to "the cell" to correct claim grammar.

Claim 48 is amended from "wherein the mammalian glycosylated polypeptide" to "wherein the glycosylated polypeptide" to correct antecedent basis. Claim 48 is also amended from "selected from the group comprising" to "selected from the group consisting of" to correct the Markush group claim language. Claim 48 is also amended to newly include "a primary amino acid sequence of a non-mammalian glycosylated polypeptide" in the Markush group. Support may be found on page 8, line 34 to page 9, line 1, which refers to the production of antibodies derived from any organism and recites, "Furthermore the method of the present invention can be used for the production of antibodies such as specific monoclonal antibodies or active fragments thereof." Further support may be found on page 19, lines 26-33, which refers to utilizing sequences that are not limited to mammalian in origin and recites,

> "Nucleotide sequences heterologous, or exogenous or foreign, to a bryophyte cell may be non-naturally occurring in cells of that type, strain or species. Thus, a nucleotide sequence may include a coding sequence of or derived from a particular type of bryophyte cell, such as *Physcomitella patens* cell, placed within the context of a bryophyte cell of a different type or species."

Claim 49 is amended from "wherein the mammalian gycosylated polypeptide" to "wherein the glycosylated polypeptide" to correct antecedent basis.

Claim 50 is amended from "wherein the mammalian gycosylated polypeptide" to "wherein the glycosylated polypeptide" to correct antecedent basis. Claim 50 is also amended to correct the spelling of "betainterferon" to "beta-interferon"; and to correct the punctuation between "follicle stimulating hormone growth factors" to "follicle stimulating hormone, growth factors"; and to correct the typographical error from "granulocyte colony stimulating" to "granulocyte colony stimulating factor." Support for the addition of "factor" may be found on page 8, lines 20-31, which recites in part, " Such pharmaceutical glycoproteins for use in mammals, including man include but are not limited to...granulocyte colony stimulating factor[.]"

Claim 51 is amended from "the said cell" to "the cell" to correct claim grammar.

Claim 55 is amended from "the said cell" to "the cell" and from "that comprises nucleic acid" to "that comprises a nucleic acid" to correct claim grammar.

Claim 58 is amended from "wherein the mammalian glycosylated polypeptide" to "wherein the glycosylated polypeptide" to correct antecedent basis; and amended from "selected from the group comprising" to "selected from the group consisting of" to correct the Markush group claim language. Claim 58 is also amended to newly include "a primary amino acid sequence of a non-mammalian glycosylated polypeptide" as a member of the Markush group. Support may be found on page 8, line 34 to page 9, line 1, which refers to the production of antibodies derived from any organism and recites, "Furthermore the method of the present invention can be used for the production of antibodies such as specific monoclonal antibodies or active fragments thereof." Further support may be found on page 19, lines 26-33, which refers to utilizing sequences that are not limited to mammalian in origin and recites,

> "Nucleotide sequences heterologous, or exogenous or foreign, to a bryophyte cell may be non-naturally occurring in cells of that type, strain or species. Thus, a nucleotide sequence may include a coding sequence of or derived from a particular type of bryophyte cell, such as *Physcomitella patens* cell, placed within the context of a bryophyte cell of a different type or species."

Claim 59 is amended to include VEGF as a member of the Markush group; and to correct punctuation from "follicle stimulating hormone growth factors" to "follicle stimulating hormone, growth factors"; and to correct the typographical error from "granulocyte colony stimulating" to "granulocyte colony stimulating factor." Support for the newly inserted "VEGF" and "factor" may be found on page 8, lines 20-31, which recite in part, " Such pharmaceutical glycoproteins for use in mammals, including man include but are not limited to...VEGF,...granulocyte colony stimulating factor[.]"

Claim 63 is amended from "wherein the mammalian glycosylated polypeptide" to "wherein the glycosylated polypeptide" to correct antecedent basis; and from "selected from the group comprising" to "selected from the group consisting of" to correct the Markush group claim language. Claim 63 is also amended to newly include "a primary amino acid sequence of a non-mammalian glycosylated polypeptide" as a member of the Markush group. Support may be found on page 8, line 34 to page 9, line 1, which refers to the production of antibodies derived from any organism and recites, "Furthermore the method of the present invention can be used for the production of antibodies such as specific monoclonal antibodies or active fragments thereof." Further support may be found on page 19, lines 26-33, which refers to utilizing sequences that are not limited to mammalian in origin and recites,

> "Nucleotide sequences heterologous, or exogenous or foreign, to a bryophyte cell may be non-naturally occurring in cells of that type, strain or species. Thus, a nucleotide sequence may include a coding sequence of or derived from a particular type of bryophyte cell, such as *Physcomitella patens* cell, placed within the context of a bryophyte cell of a different type or species."

Claim 64 is amended from "wherein the mammalian glycosylated polypeptide" to "wherein the glycosylated polypeptide" to correct antecedent basis.

Claim 65 is amended to correct dependency (from claim 43 to claim 63) and to correct the following typographical errors: from "wherein the mammalian glycosylated polypeptide" to

"wherein the glycosylated polypeptide" to correct antecedent basis; and from "proinsuin" to "proinsulin" to correct a spelling error; and from "follicle stimulating hormone growth factors" to "follicle stimulating hormone, growth factors" to correct punctuation in the Markush group; and from "granulocyte colony stimulating" to "granulocyte colony stimulating factor" to a correct spelling error; and from "betaglucocarebrosidase" to "betaglucocerebrosidase" to correct a spelling error.

Claim 67 is amended to recite,

> "A set of nucleic acid vectors suitable for producing at least a transformed bryophyte cell that comprises i) a dysfunctional fucosyl transferase nucleotide sequence and ii) a dysfunctional xylosyl transferase nucleotide sequence, wherein said set of nucleic acid vectors comprises i) a first nucleic acid sequence that is specifically targeted to an endogenous fucosyl transferase nucleotide sequence and ii) a second nucleic acid sequence that is specifically targeted to an endogenous xylosyl transferase nucleotide sequence."

Support for amended claim 67 may be found on page 6, lines 33-36, which recites, "According to the present invention there is provided a transformed bryophyte cell that comprises i) a dysfunctional fucosyl transferase nucleotide sequence and ii) a dysfunctional xylosyl transferase nucleotide sequence." Referring to page 10 lines 20-24, the nucleic acid vectors include, "i) a first nucleic acid sequence that is specifically targeted to an endogenous fucosyl transferase nucleotide sequence and ii) a second nucleic acid sequence that is specifically targeted to an endogenous xylosyl transferase nucleotide sequence."

Claim 69 is amended to recite, "A set of nucleic acid vectors according to claim 67, further including a polynucleotide that encodes a glycosylated polypeptide." Support may be found on page 8, lines 12-20, which recites,

> "Alternatively, the bryophyte cell may be transformed severally, that is simultaneously or over time with nucleotide sequences coding for at least a primary protein sequence of interest...that require mammalian glycosylation patterns to be placed on them in accordance with the methods of the invention as described herein."

Claim 70 is amended recite,

> "A set of nucleic acid vectors according to claim 67, further including a polynucleotide that encodes a functional mammalian galactosyl transferase for use in a method of producing at least a bryophyte cell wherein fucT and xylT activity is substantially reduced, that comprises introducing into said cell i) a first nucleic acid sequence that is specifically targeted to an endogenous fucosyl transferase nucleotide sequence and ii) introducing into said cell a second nucleic acid sequence that is specifically targeted to an endogenous xylosyl transferase nucleotide sequence."

Support may be found on page 9, lines 1-10, which recites in part,

> "[A] transformed bryophyte cell that comprises i) a dysfunctional fucosyl transferase nucleotide sequence and ii) a dysfunctional xylosyl transferase nucleotide sequence and iii) a nucleotide sequence operably linked to an exogenous promoter that drives expression in the said bryophyte cell wherein said nucleotide sequence encodes a functional mammalian galactosyl transferase that is expressed in the bryophyte cell."

Further support may be found on page10, lines 16-24, which recites in part,

> "[A] method of producing at least a bryophyte cell wherein fucT and xylT activity is substantially reduced that comprises introducing into the said cell i) a first nucleic acid sequence that is specifically targeted to an endogenous fucosyl transferase nucleotide sequence and ii) a second nucleic acid sequence that is specifically targeted to an endogenous xylosyl transferase nucleotide sequence."

Claim 71 is amended to recite, "A set of nucleic acid vectors according to claim 70, wherein said polynucleotide encodes a mammalian galactosyl transferase." Support may be found on page 11, lines 23-24, which recite in part, "[S]aid nucleic acid encodes at least one mammalian galactosyl transferase."

Claim 72 is amended from "A host cell containing a nucleic acid vector according to claim 67" to "A host cell containing the set of nucleic acid vectors according to claim 67" to correct antecedent basis.

Claim 75 is amended from "incorporating said nucleic acid vector into the cell" to "incorporating said set of nucleic acid vectors into the cell" to correct antecedent basis.

Claim 76 is amended from "Use of a nucleic acid vector according to claim 67" to "Use of the set of nucleic acid vectors according to claim 67" to correct antecedent basis.

Claim 79 is amended from "incorporating a nucleic acid vector according to claim 67" to "incorporating the set of nucleic acid vectors according to claim 67" to correct antecedent basis.

Claim 80 is newly presented and recites, "A set of nucleic acid vectors according to claim 71, wherein said polynucleotide encodes a human beta-1,4 galactosyl transferase." Support may be found on page 11, line 21-28, which recites in part,

> "[S]aid nucleic acid encodes at least one mammalian galactosyl transferase polypeptide. In this embodiment of the invention the at least one mammalian galactosyl transferase polypeptide is preferably a beta-1,4 galactosyl transferase (beta-1,4 galT) and most preferably is a human beta-1,4 galactosyl transferase nucleotide sequence"

Restriction Requirement

The above identified patent application has been examined for restriction purposes only and has not been examined on the merits; however, specific reference to Schaefer et al. was alleged to anticipate claims 51-66 and 79 in support of the restriction requirement.

In the Office Action, the Examiner restricts the claims into three distinct and independent inventions under 35 U.S.C. §121. More specifically, the Examiner has set forth the following groups:

Group Number	Claims	Subject Matter
I	38-50 and 78	A transformed bryophyte cell, No classification provided
II	51-66 and 79	A method of producing at least one bryophyte cell wherein fucT and xylT activity is substantially reduced and said cell further comprises a nucleotide sequence operably linked to an exogenous promoter that drives expression in said bryophyte cell, No classification provided
III	67-77	A nucleic acid vector suitable for producing at least a bryophyte cell wherein fucosyl and xylosyl transferase nucleotide sequences are dysfunctional, No classification provided

The Examiner argues Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because under PCT Rule 13.2, they lack the same or corresponding special technical feature for the following reasons: The technical feature linking Groups I-III appears to be that they all relate to a transformed bryophyte cell and nucleic acid vector suitable for

producing a bryophyte cell expressing heterologous polypeptides. However, transformed bryophyte cell and nucleic vector suitable for producing a bryophyte cell expressing heterologous polypeptides were known in the art. For example, Schaefer et al., 2001 teach transformed bryophyte cell and nucleic acid vector suitable for producing a bryophyte cell expressing heterologous polypeptides (pages 1433-1434), which anticipates claims 51-66 and 79. Therefore Groups I-III share no special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art. Accordingly, Groups I-III are not so linked by the same or corresponding special technical feature as to form a single general inventive concept.

The Examiner argues that in addition to the arguments with respect to PCT Rules 13.1 and 13.2, each invention has acquired a separate status in the art due to their recognized divergent subject matter and thus, searching more than one invention would be a burden on the Office.

In addition, the Examiner further requires an election of a single species from a list of 51 glycosylated peptides shown in pages three to five of the Office Action dated September 5, 2007. Although the Examiner admits that Groups I and II, (claims 38-49, 51-57, 60-64 and 66) are generic, election of a single species is required because searching all species would impose a serious burden on the Examiner.

Applicants' Response to Restriction Requirement

For completeness, Applicants elect the invention of **Group I** (claims 38-50 and 78) directed towards a transformed bryophyte cell and elect the species **VEGF**. Applicants' election is provided with traverse.

Support for the present election of Group I and VEGF may be found throughout the application including the specification as originally filed. Specifically, support may be found on page 45, line 25 through 46, line 32, which describes the purification and analysis of human VEGF expressed in transiently transformed *Physcomitrella* protoplasts. This election is made with traverse because of the commonality of the subject matter of the three Groups and species.

1. The Examiner Has Mischaracterized Applicants' Invention as a Simple Transformed Cell and Nucleic Acid Vector for the Preparation of Heterologous Polypeptides, Whereas the Invention Relates to a Complex Double Knock-out System that Affects the Glycosylation Capabilities of the Transformed Bryophyte Cell.

Although examination has only been performed for the basis of restriction purposes, the Examiner states,

> "[T]he technical feature linking Groups I-III appears to be that they all relate to a transformed bryophyte cell and nucleic acid vector suitable for producing a bryophyte cell expressing heterologous polypeptides. However transformed bryophyte cell and nucleic acid vector suitable for producing a bryophyte cell expressing heterologous polypeptides were known in the art. For example Schaefer et al., 2001 teach a transformed bryophyte cell and nucleic acid vector suitable for producing a bryophyte cell expressing heterologous polypeptides (pages 1433-1434), which anticipates claims 51-66 and 79."

The contribution to the state of the art advanced by the present application is not merely a transformed bryophyte cell and nucleic acid vector for producing a heterologous protein, but instead is a complex double-knockout system that affects the glycosylation of proteins introduced into a bryophyte system. Specifically referring to page 7, lines 16-22 of the present application,

> "Dysfunctional" as used herein means that the nominated transferrase nucleotide sequences of fucosyl transferase (fucT) and xylosyl transferase (xylT) are substantially incapable of encoding mRNA that codes for functional fucT and xylT proteins that are capable of modifying plant N-linked glycans with plant like glycosylation patterns comprising 1,3 linked fucosysl and 1, 2 linked xylosyl residues."

With respect to Group I (claims 38-50 and 78), the present invention includes a transformed bryophyte cell including a dysfunctional fucosyl transferase nucleotide sequence and a dysfunctional xylosyl transferase nucleotide sequence. With respect to Group II (claims 51-66

and 79), the present invention includes a method of producing at least one bryophyte cell wherein fucT and xylT activity is substantially reduced, the method including introducing into the cell a first nucleic acid that is specifically targeted to an endogenous fucosyl transferase nucleotide sequence and introducing into the cell a second nucleic acid sequence that is specifically targeted to an endogenous xylosyl transferase nucleotide sequence. With respect to Group III (claims 67-77), the present invention includes a nucleic acid vector suitable for producing at least a bryophyte cell wherein fucosyl and xylosyl transferase nucleotide sequences are dysfunctional.

Now turning to the cited reference, Schaefer et al. does not disclose a system with a dysfunctional fucosyl transferase nucleotide sequence or a dysfunctional xylosyl transferase nucleotide sequence. Although the reference does broadly discuss transformations, Schaefer et al do not discuss the reduction, elimination or substitution of endogenus glycosylation capabilities. Thus unlike the present invention, the effect of glycosylation is not controlled in Schaefer et al.

In view of Applicants' remarks and the commonality of subject matter, Applicants respectfully request the Examiner rejoin Groups I-III or in the alternative Groups I and II or Groups I and III.

2. Examination of Groups I-III Would Not Seriously Burden the Examiner.

The Examiner has also indicated that examination of Groups I-III would seriously burden the examiner. Restriction is proper when the search and examination of patentably distinct claims would place a serious burden on the Examiner (MPEP § 803).

Although Groups I-III are patentably distinct, Groups I-III are directed towards overlapping subject matter and would therefore not seriously burden the Examiner. Groups I-III are directed towards cells, methods and nucleic acid vectors that address the common subject matter of bryophyte systems providing a dysfunctional fucosyl transferase nucleotide sequence and a dysfunctional xylosyl transferase nucleotide sequence. Thus any search and examination would likely address such features and therefore the combination of Groups I-III would not seriously burden the Examiner.

Based on the commonality of the subject matter of the three groups Applicants respectfully request that the Examiner rejoin the claims of Groups I-III into a single group. In the alternative, Applicants respectfully request Groups I and II or Groups I and III be rejoined.

3. Examination of Multiple Species Would Not Seriously Burden the Examiner.

The Examiner has identified 51 species of glycosylated polypeptides for Groups I and II, referring to claims 50, 59 and 65 and requires election of the glycosylated polypeptide to a single species. Restriction is proper when the search and examination of patentably distinct claims would place a serious burden on the Examiner (MPEP § 803). For completeness, Applicants elect the species VEGF, with traverse.

Although the provided species are patentably distinct, the listed species are directed towards overlapping subject matter and would therefore not seriously burden the Examiner. The provided species are directed towards glycosylated polypeptides and their application in a bryophyte system having a dysfunctional fucosyl transferase nucleotide sequence and a dysfunctional xylosyl transferase nucleotide sequence. Thus any search and examination performed by the Examiner would naturally address various glycosylated peptides and their applicability to the bryophyte system as described would therefore not seriously burden the Examiner.

Based on the commonality of the subject matter, Applicants respectfully request that the Examiner permit the rejoining of glycoslyated polypeptides and withdraw the species election requirement.

In view of the amendments and arguments set forth above, Applicants respectfully request the rejoining of Groups I-III and respectfully submit the claims are in condition for allowance.

Respectfully submitted,

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Date

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